Associations between Cannabis Use and Physical Health Problems in Early Midlife: A Longitudinal Comparison of Persistent Cannabis versus Tobacco Users

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Importance: Following major policy changes in the United States, policy makers, clinicians, and the general public seek information about whether recreational cannabis use is associated with physical health problems later in life.

Objective: To test associations between cannabis use over twenty years and a variety of physical health indices at early midlife.

Design: A 38-year, prospective, longitudinal study of a representative birth cohort.

Setting: The Dunedin Multidisciplinary Health and Development Study of New Zealand.

Participants: The study included 1,037 male and female participants.

Exposure: We assessed frequency of cannabis use and also cannabis dependence at ages 18, 21, 26, 32, and 38 years.

Main Outcomes and Measures: We obtained laboratory measures of physical health (periodontal health, lung function, systemic inflammation, and metabolic health), as well as self-reported physical health, at ages 26 and 38.

Results: Cannabis use was associated with poorer periodontal health at age 38 and within-individual decline in periodontal health from age 26-38. For example, 55.61% of those with 15+ joint years had periodontal disease, compared with 13.53% of those who never used cannabis. Cannabis use was unrelated to other physical health problems, however. Unlike cannabis use, tobacco use was associated with worse lung function, systemic inflammation, and metabolic health at age 38, as well as within-individual decline in health from age 26 to 38.

Conclusions and Relevance: Cannabis use for up to 20 years is associated with periodontal disease but is not associated with other physical health problems in early midlife.

Associations between Cannabis Use and Physical Health Problems in Early Midlife: A Longitudinal Comparison of Persistent Cannabis versus Tobacco Users

Following policy changes in the United States, policy makers, clinicians, and the public seek information about whether recreational cannabis use is associated with physical health problems later in life. Two recent reviews found that persistent cannabis use is associated with relatively few physical health problems, the possible exceptions being cardiovascular risks and bronchitis.[1,2] Firm conclusions cannot be drawn, however, due to methodological shortcomings.[3] Most studies are cross-sectional and/or rely on self-reported health.[4-11] These designs cannot resolve the temporal association between cannabis use and health, nor can they address the possibility that cannabis users may have biased perceptions of their health. Longitudinal studies with laboratory-based measures and physical examinations are needed.

Few longitudinal studies have characterized cannabis users' long-term health using objective, laboratory-based indices and examinations (**Table 1**). Each study focused on a single domain of physical health, providing an important but incomplete picture. In a population-representative study of individuals followed from birth to age 38, we tested associations between cannabis use over 20 years and multiple domains of physical health in early midlife. We selected the following health domains based on prior research,[1-3] demonstrated capacity to predict disease morbidity and mortality,[21-23] and biological plausibility of an effect of cannabis by early midlife: periodontal health, lung function, systemic inflammation, and metabolic risk. First, we tested whether cannabis use from age 18-38 was associated with age-38 health. Second, we tested whether cannabis use from age 26-38 was associated with within-individual health decline using

the same measures of health at both ages. To provide a benchmark for comparison, we also tested associations between tobacco use and physical health.

Methods

Participants

Participants are members of the Dunedin Study, a longitudinal investigation of health and behavior in a representative birth cohort.[24] Study members (N=1,037; 91% of eligible births; 52% male) were all individuals born between 1972-1973 in Dunedin, New Zealand, who were eligible for the longitudinal study based on residence in the province at age 3 and who participated in the first follow-up at age 3. The cohort represents the full range of SES in the general population of New Zealand's South Island and is primarily white.[24] On adult health, the cohort matches the NZ National Health & Nutrition Survey (e.g., body mass index, smoking, general practitioner visits).[24] Assessments occurred at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and, most recently, 38 years, when 95% of the 1,007 living Study members took part. At each assessment phase, study members are brought to the Dunedin Research Unit for interviews and examinations. The Otago Ethics Committee approved each phase of the study. Written consent was obtained from all participants.

Analyses were limited to 947 study members with age-38 laboratory health data, as 46 study members were not seen at age 38, 30 were deceased, and 14 had field interviews that did not include laboratory measurements/examinations. There were no differences between those with and without age-38 health data on childhood health ($F=1.42$, $p=.23$), cigarettes smoked per day at age 18 ($F=1.28$, $p=.26$), or frequency of cannabis use at age 18 ($F=2.85$, $p=.092$).

Table 2 shows characteristics of participants according to tobacco and cannabis exposure, including sex, childhood health,[25] and childhood SES,[26] which were available as covariates.

Tobacco Pack-Years

Cumulative tobacco exposure was calculated from the reported number of cigarettes smoked per day at each assessment divided by 20 and multiplied by number of years smoked at that rate through age 38. One pack-year reflects the equivalent of 20 cigarettes a day for one year. Mean pack-years for those with age-38 health data was 6.17 (SD=8.69). For analyses testing associations between pack-years from age 26-38 and change in physical health using the same measure of health at both ages, we estimated pack-years in the same way except estimates represented cigarette use at ages 26-38 (M=3.30, SD=5.12).

Cannabis Joint-Years

"Pack-years," which combines information about smoking duration and intensity, is the most commonly used exposure in tobacco studies.[27] We created a parallel variable that indexes cannabis smoking. Cumulative joint-years was estimated using self-reported frequency of cannabis use over the past year (0-365 days) at ages 18-38. One joint-year reflects the equivalent of daily cannabis use for one year. Mean joint-years between ages 18-38 for those with age-38 health data was 1.99 (SD=4.43). For analyses of health change from age 26-38, we estimated joint-years in the same way except estimates represented cannabis use at ages 26-38 (M=1.18, SD=3.00).

Persistent Cannabis Dependence

Because our prior reports have characterized cannabis users in terms of persistent dependence over time,[28,29] we also report this variable as our exposure. We assessed past-year dependence at ages 18-38 with the Diagnostic Interview Schedule[30,31] following Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria.[32,33] Persistent dependence was defined as the number of study waves out of five at which a study member met criteria for dependence:

never used cannabis at any study wave; used at least once between ages 18-38 but never diagnosed; diagnosed at 1 wave; diagnosed at 2 waves; and diagnosed at 3+ waves. For analyses of health change from age 26-38, we again defined persistent dependence as the number of study waves at which a study member met criteria for dependence but only used cannabis data from ages 26-38.

Age-38 Physical Health

Physical examinations were conducted during the age-38 assessment day, with blood draws between 4:15-4:45 p.m.[34] **Table 3** describes each health outcome. We report health outcomes scored as dichotomous clinical outcomes for clinical relevance and also scored as continuously distributed outcomes, because continuous measures are more sensitive to variation. Positively skewed continuous outcomes (combined attachment loss, inflammation, triglycerides, glycated hemoglobin) were log-transformed prior to analysis.

Age-26 Physical Health

The age-38 health measures were also administered at age 26 using the same procedures with two exceptions.[34] First, periodontal measurements were made using a half-mouth design.[12] Second, serum C-reactive protein was assayed with a sensitivity level of 1 mg/l.[45] Due to this lower sensitivity, C-reactive protein scores in the top quintile of the distribution were designated as elevated.

Statistical Analysis

To test whether cannabis use was associated with poor health in early midlife, we tested the bivariate association between cannabis use from age 18-38 and age-38 health (Table 4, Model 1) and subsequently added tobacco pack-years from age 18-38 as a covariate (Table 4, Model 2). To test whether cannabis use from age 26-38 was associated with health decline using

the same measure of health at both ages, we tested the bivariate association between cannabis use from age 26-38 and age-38 health (Table 5, Model 1) and subsequently added age-26 health as a covariate (Table 5, Model 2), followed by tobacco pack-years from age 26-38 as an additional covariate (Table 5, Model 3). All analyses controlled for sex.

Statistical analyses tested associations of tobacco pack-years (a continuous variable), cannabis joint-years (a continuous variable), and cannabis dependence (a 5-level ordinal variable) with both dichotomous and continuous health outcomes. We analyzed dichotomous outcomes using Poisson regression models to derive relative risks and continuous outcomes using ordinary-least-squares regression to derive beta coefficients. We standardized continuous variables prior to conducting statistical tests. Therefore, relative risks and beta coefficients can be interpreted as the increase in risk of the outcome, given a 1 SD increase in pack-years or joint-years. To aid interpretation of relative risks and beta coefficients associated with continuous pack-years and joint-years, we report unstandardized, sex-adjusted means for health outcomes as a function of tobacco and cannabis use, with study members grouped according to pack-years and joint-years in 5-year increments (Table 4).

Results

Tobacco Smoking and Health

Bivariate associations showed that tobacco pack-years was associated with worse health for eight of twelve health outcomes (both categorically- and continuously-scored versions of the following): periodontal health, lung function, inflammation, metabolic syndrome, high density lipoprotein, triglycerides, HbA1c, and self-reported health (**Table 4, Model 1**). For example, 12.26% of individuals who never used tobacco had periodontal disease (1+ sites with >5mm attachment loss), compared with 52.89% of individuals with 15+ pack-years (**Table 4**).

Statistical tests showed that for every standard deviation increase in pack-years (~9 pack-years), relative risk for periodontal disease increased by 1.63 ($p<.001$). Associations remained significant for all eight of these health outcomes after controlling for cannabis joint-years (**Table 4, Model 2**) and after additionally controlling for childhood health and SES (when considering either the continuous or categorical version of the outcome) (**Supplemental Table 1, Model 3**). Findings are consistent with prior research.[12-14,18,46-51]

Cannabis Use and Health

Bivariate associations showed that cannabis joint-years was associated with worse health for three of twelve health outcomes (either the continuous or categorical version of the outcome): periodontal health, lung function, self-reported health (**Table 4, Model 1**). Adverse associations remained significant for two outcomes (periodontal health, lung function) after controlling for tobacco pack-years (**Table 4, Model 2**) and after additionally controlling for childhood health and SES (**Supplemental Table 1, Model 3**). However, poorer lung function (FEV_1/FVC) among cannabis users was probably not indicative of airway obstruction, as joint-years (unlike tobacco pack-years) was unrelated to reduced FEV_1 (**Supplemental Table 2**). Rather, reduced FEV_1/FVC among cannabis users was attributable to higher FVC values. It is unclear whether higher FVC values reflect better health.

Unlike tobacco, cannabis joint-years was associated with slightly smaller waist circumference and lower BMI. Further, after adjusting for tobacco pack-years (**Table 4**, **Model 2**), associations emerged between joint-years and better HDL, triglycerides, and glycated hemoglobin. Joint-years was not associated with lower risk of metabolic syndrome, however.

Results for persistent cannabis dependence (and results for persistent regular cannabis use, **Supplemental Table 3**) were nearly identical to those for joint-years. Bivariate associations

showed that persistent dependence was associated with worse health for three of twelve outcomes (continuous or categorical): periodontal health, lung function, self-reported health. Associations remained significant for one of those three (periodontal health) after controlling for tobacco pack-years (**Table 4, Model 2**) and after additionally controlling for childhood health and SES (**Supplemental Table 1, Model 3**). **Supplemental Table 4** provides a descriptive summary of the aforementioned findings.

Periodontal health was the only aspect of health that showed a robust adverse association in analyses of both persistent dependence and joint-years. Post-hoc analyses showed that cannabis users brushed and flossed less than others, and were more likely to be alcohol dependent (**Supplemental Table 5**). However, associations between cannabis use and poor periodontal health remained significant after controlling for tobacco pack-years, childhood health and SES, brushing and flossing, and alcohol dependence (**Supplemental Table 6**).

The general lack of association between persistent cannabis use and poor physical health may surprise. One explanation is that healthy youth select into cannabis use. Our test showed no correlation between cannabis use and childhood health (**Table 2**). Another explanation is cannabis users may have healthier adult lifestyles. Tests showed that cannabis was not associated with more physical activity or with a diet of fruits and vegetables (**Supplemental Table 5**). The lacking associations between cannabis use and poor physical midlife health could not be attributed to better initial health, more physical activity, better diet, or less alcohol abuse.

Tobacco and Cannabis Use and Change in Health

Tobacco pack-years from age 26-38 was associated with worsening periodontal health, lung function, systemic inflammation, and metabolic health **(Table 5, Model 2**). For example, pack-years from age 26-38 was associated with increased risk of age-38 metabolic syndrome

after accounting for age-26 metabolic syndrome (**Table 5, Model 2:** RR=1.18, p=.021). Tobacco users also self-reported worse health at 38, and this association persisted after accounting for age-26 self-reported health (**Table 5, Model 2**).

Like tobacco use, cannabis use was associated with decline in periodontal health and lung function (measured continuously) (**Table 5, Model 2**), even after accounting for tobacco pack-years from 26-38 (**Table 5, Model 3**). Again, however, decline in FEV_1/FVC was probably not attributable to airway obstruction, as cannabis use was not robustly associated with decline in FEV_1 (**Supplemental Table 7**). Cannabis use was not associated with deteriorating health in other domains.

Discussion

Findings showed that, in general, cannabis use over 20 years was unrelated to health problems in early midlife. Across several domains of health (periodontal, lung function, inflammation, and metabolic health), clear evidence of an adverse association with cannabis use was apparent for only one: periodontal health. Cannabis use from age 26-38 was not associated with within-individual health decline during this 12-year period, with the exception of periodontal health. By comparison, tobacco use was associated with worse periodontal health, lung function, systemic inflammation, HDL, triglycerides, and glucose control in early midlife, as well as health decline from age 26-38.

Findings showed that cannabis use was associated with slightly better metabolic health (smaller waist circumference, lower BMI, better lipid profiles and glucose control). The majority of these associations emerged only after controlling for tobacco use, however. Effects were small but intriguing given similar reports from cross-sectional studies,[4,8,9,52-54] and that endocannabinoids appear to be involved in the regulation of metabolism.[55] Several studies have

shown that overweight patients who took a synthetic cannabinoid-1 receptor blocker, rimonabant, evidenced reduced waist circumference and improved lipid profiles.[56,57] It is unclear, however, if and how recreational cannabis use (and plant-based cannabinoids) might impact metabolic health. Cannabinoid pharmacology is more complex than commonly believed,[58] and biological arguments can be made for cannabis-related worsening or improvement of metabolic health.[9,59] The only other longitudinal study to characterize cannabis users' metabolic health found no association,[19] and our finding of a small association mainly emerged after controlling for tobacco use. Moreover, cannabis use was not associated with reduced risk of metabolic syndrome. Thus, current evidence suggests that recreational cannabis use is unlikely to improve metabolic health in the general population.

In at least two instances, we found no association between cannabis and poor health when we might have expected one. In the first instance, we found no association between cannabis and reduced FEV_1 (**Supplemental Table 3**), which is somewhat puzzling given that tobacco use is associated with reduced FEV_1.[13,14] An association between cannabis and reduced FEV_1 could emerge with greater exposure to cannabis.[13] Nonetheless, given no evidence of reduced FEV_1 among cannabis users, our finding of lower FEV_1/FVC among cannabis users probably did not indicate airway obstruction. Rather, reduced FEV_1/FVC appeared to reflect cannabis users' slightly larger forced vital capacity (FVC). This association with larger FVC, also reported elsewhere,[13] is not understood. Overall, findings are consistent with a recent review that concluded that there is little evidence that cannabis affects FEV_1 and airway obstruction.[60] In the second surprising instance, we found no association between cannabis and cardiovascular risks (e.g., high blood pressure, worse cholesterol), which may appear at-odds with evidence that cannabis use increases risk for cardiovascular complications,[61-63] even among young healthy

individuals.[64] Our somewhat disparate findings are reconciled by evidence that cannabis-related cardiovascular complications are likely acute cannabis effects.[19,53,61,63]

Although we found that cannabis users were generally no worse off than non-users on nearly all health indices, they did have worse periodontal health. Cannabis use was associated with attachment loss, which can result in tooth loss.[12,51] A similar association was observed for tobacco use, consistent with previous research.[12,51,65] Tobacco's effect on periodontal disease is thought to be mediated through increased inflammation and vasoconstriction,[65] which may or may not be the case for cannabis. Cannabis use was not associated with systemic inflammation here or elsewhere,[18,54] but prior research has shown that cannabis can induce vasoconstriction.[66,67]

This study has limitations. First, cannabis joint-years was based on self-reports collected at ages 18-38. Validation of cannabis use through laboratory measures could have helped detect cannabis users who denied use. Underreporting due to reluctance to admit to illegal drug use is unlikely, however, because study members, interviewed repeatedly over the course of their lives, have learned to trust our confidentiality guarantee. Second, disentangling cannabis and tobacco use is challenging. In New Zealand, cannabis is not typically mixed with tobacco,[10] but most participants who used cannabis also smoked cigarettes. Although we controlled for tobacco use, imperfect control might bias results toward finding spurious associations between cannabis use and poor health. We note, however, that all poor health outcomes, apart from periodontal disease, were unrelated to cannabis use. Third, our findings are based on a single New Zealand cohort who began using cannabis in the 1980s-90s. Although our findings are generally consistent with longitudinal studies of United States samples (**Table 1**), tetrahydrocannabinol (THC; the primary psychoactive ingredient in cannabis) content has increased since then.[2] If

health associations are mediated by THC, we may have underestimated the cannabis-health association. Fourth, our conclusions are limited to a specific set of health problems assessed in early midlife. Though this is the most comprehensive study to date, cannabis use may be associated with health problems not studied here or that tend to emerge later in life, such as cancer. Fifth, we compared findings for cannabis against findings for tobacco. Our intent in doing so was to allay concerns that our study's methods might be unable to detect health problems. We acknowledge that participants acquired more tobacco pack-years than cannabis joint-years, with most cannabis users using for fewer than five years. Greater tobacco exposure may explain health decline associated with tobacco but not cannabis use. If patterns of cannabis use shift, and more users begin to use cannabis as they do tobacco (i.e., multiple joints per day), cannabis-associated health problems might emerge. Finally, our study cannot comment on the health effects of cannabis in older adults or the safety of medical marijuana use in patients who are already unwell.

This study has a number of implications. First, cannabis use for up to 20 years is not associated with a specific set of physical health problems in early midlife. The sole exception is that cannabis use is associated with periodontal disease. Second, cannabis use for up to 20 years is not associated with net metabolic benefits (i.e., lower rates of metabolic syndrome). Third, results should be interpreted in the context of prior research showing that cannabis use is associated with accidents and injuries, bronchitis, acute cardiovascular events, and, possibly, infectious diseases and cancer, as well as poor psychosocial and mental health outcomes.[1-3,20,28,29,60,68-70]

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Table 1. Longitudinal studies with objective, laboratory-based indices and physical examinations of cannabis users' long-term physical health.

Study	Analysis Sample	Age (or Age Range) at Baseline	Age (or Age Range) at Follow-up	Outcomes	Finding
Periodontal Health					
Thomson et al.[12]	Dunedin Multidisciplinary Health and Development Study: 903 men and women	18	32	Periodontal attachment loss	Cannabis use was associated with attachment loss, even after adjusting for tobacco use, sex, SES, dental service use, and plaque.
Lung Function[a]					
Pletcher et al.[13]	Coronary Artery Risk Development in Young Adults (CARDIA): 5,016 men and women	18-30 (M=25)	Participants were followed up to 20 years from baseline	Forced expiratory volume (FEV_1) and forced vital capacity (FVC)	In adjusted analyses (covariates included, but were not limited to, demographic factors and tobacco exposure), there was a non-linear association of cannabis exposure with FEV_1 and FVC. At low levels of cannabis exposure, FEV_1 and FVC increased. At higher levels of cannabis exposure, associations reversed (FEV_1) or leveled (FVC).

Table 1 Continued.

Study	Analysis Sample	Age (or Age Range) at Baseline	Age (or Age Range) at Follow-up	Outcomes	Finding
Hancox et al.[14]	Dunedin Multidisciplinary Health and Development Study: 779 men and women	15	32	Forced expiratory volume (FEV_1), forced vital capacity (FVC), and airflow obstruction (FEV_1/FVC)	In adjusted analyses (covariates included, but were not limited to, demographic factors, tobacco use, and baseline level of the outcome), cannabis use was associated with higher FVC but was not associated with FEV_1 or FEV_1/FVC.
Taylor et al.[15]	Dunedin Multidisciplinary Health and Development Study: 859-930 men and women	18	26	Forced expiratory volume (FEV_1) and airflow obstruction (FEV_1/FVC)	In adjusted models (covariates included, but were not limited to demographic factors and tobacco use), cannabis exposure was associated with reduced FEV_1 but was not associated with FEV_1/FVC.
Tashkin et al.[16]	255 men and women	M=33	Up to 8 years from baseline	Forced expiratory volume (FEV_1)	Cannabis use was not associated with decline in FEV_1.

Table 1 Continued.

Study	Analysis Sample	Age (or Age Range) at Baseline	Age (or Age Range) at Follow-up	Outcomes	Finding
Sherrill et al.[17]	Tucson longitudinal study of airways obstructive disease: 856 men and women with pulmonary data from at least two assessments	15-60	Up to 6 years from baseline	Forced expiratory volume (FEV_1) and airflow obstruction (FEV_1/FVC)	In adjusted models (covariates included, but were not limited to, demographic factors), previous cannabis use was associated with reduced FEV_1 and FEV_1/FVC, whereas current cannabis use was associated with a non-significant increase in FEV_1 and was not associated with FEV_1/FVC.
Systemic Inflammation					
Costello et al.[18]	Great Smoky Mountains Study: 1334 boys and girls	9-16	21	C-reactive protein	Cannabis use was not associated with later C-reactive protein, controlling for past C-reactive protein. C-reactive protein predicted later cannabis use and cannabis use disorder controlling for previous cannabis use and cannabis use disorder, but not after controlling for age, sex, race, body mass index, SES,

					health, medications, and psychiatric disorder.

Table 1 Continued.

Study	Analysis Sample	Age (or Age Range) at Baseline	Age (or Age Range) at Follow-up	Outcomes	Finding
Metabolic Health					
Rodondi et al.[19]	Coronary Artery Risk Development in Young Adults (CARDIA): 3,617 men and women	18-30	Participants were followed to 15 years from baseline.	Body mass index, waist circumference, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, fasting plasma glucose	In unadjusted analyses, cannabis use was associated with larger waist circumference, higher systolic blood pressure, and higher triglycerides. In adjusted analyses (covariates included, but were not limited to, demographic factors; tobacco, alcohol, and illicit drug use; and baseline level of the outcome variable), all associations became non-significant.

Note. [a]We report on spirometry measures (FEV_1, FVC, and FEV_1/FVC ratio). These are the most commonly reported measures of lung function in longitudinal studies, and FEV_1/FVC is the most sensitive measure for assessing airway remodeling in a large cohort. A few longitudinal studies of cannabis also included other measures of respiratory health. For a recent report from the Dunedin Study on cannabis and respiratory symptoms (e.g., morning cough, sputum production, wheeze), see Hancox et al.[20]

Table 2. Characteristics of study members according to tobacco and cannabis use from age 18 to 38 years.

	Tobacco Pack-Years (Ages 18-38)[a]						
	% or Mean (SD) as a Function of Pack-Years					Statistical Tests[b]	
Correlate	Never Used N=461	<5y N=137	5 to <10y N=83	10 to <15y N=92	15+y N=172	r	p
Sex (% Male)	52%	39%	42%	50%	58%	0.07	0.034
Childhood Health[c]	0.04 (0.97)	0.03 (0.86)	0.10 (1.00)	0.05 (0.89)	-0.15 (1.02)	-0.07	0.045
Childhood SES[c]	0.17 (0.98)	0.15 (0.97)	0.01 (0.87)	-0.33 (0.90)	-0.29 (1.03)	-0.20	<.001
Cannabis Joint-Years Age 18 to 38	0.61 (2.39)	1.28 (3.17)	2.04 (3.82)	2.67 (4.35)	5.84 (6.83)	0.48	<.001
Tobacco Pack-Years Age 18 to 38	0.00 (0.00)	2.25 (1.65)	7.44 (1.38)	12.50 (1.50)	21.82 (5.40)	-	-

	Cannabis Joint-Years (Ages 18-38)[a]						
	% or Mean (SD) as a Function of Joint-Years					Statistical Tests[b]	
Correlate	Never Used N=265	<5y N=552	5 to <10y N=42	10 to <15y N=44	15+y N=37	r	p
Sex (% Male)	38%	50%	71%	73%	78%	0.21	<.001
Childhood Health[c]	0.01 (0.92)	0.03 (0.97)	0.03 (0.98)	0.01 (0.90)	-0.07 (0.94)	-0.02	.61
Childhood SES[c]	0.05 (1.01)	0.10 (0.99)	-0.19 (0.93)	-0.34 (0.85)	-0.42 (0.96)	-0.13	<.001
Cannabis Joint-Years Age 18 to 38	0.00 (0.00)	0.63 (1.05)	7.38 (1.27)	12.54 (1.43)	17.83 (2.13)	-	-
Tobacco Pack-Years Age 18 to 38	1.97 (5.27)	6.07 (7.84)	12.63 (9.95)	16.34 (8.86)	19.34 (11.96)	0.48	<.001

Table 2 Continued.

	Persistent Cannabis Dependence (Ages 18-38)[a]						
	% or Mean (SD) as a Function of Persistence of Cannabis Dependence					Statistical Tests[b]	
Correlate	Never Used N=265	Used, No Dx N=504	1 Dx N=85	2 Dx N=43	3+ Dx N=43	r	p
Sex (% Male)	38%	49%	69%	65%	84%	0.22	<.001
Childhood Health[c]	0.01 (0.92)	0.03 (0.98)	0.02 (0.91)	-0.09 (0.96)	0.11 (0.89)	0.01	.82
Childhood SES[c]	0.05 (1.01)	0.09 (0.98)	-0.12 (1.03)	-0.13 (0.99)	-0.40 (0.86)	-0.10	.004
Cannabis Joint-Years Age 18 to 38	0	0.92 (2.37)	4.80 (5.66)	9.32 (5.36)	13.94 (4.70)	0.72	<.001
Tobacco Pack-Years Age 18 to 38	1.97 (5.27)	5.84 (7.76)	9.64 (9.33)	15.52 (9.22)	20.58 (10.05)	0.51	<.001

Note. a. Of the N=947 with age-38 health data, two study members were missing tobacco pack-years data, and seven study members were missing cannabis joint-years data. b. We report Pearson correlations between correlates and tobacco pack-years (a continuous variable), cannabis joint-years (a continuous variable), and persistent cannabis dependence (a 5-level variable). c. Scores were standardized to M=0.00, SD=1.00. Children's overall health at ages 3, 5, 7, 9, 11, 13, and 15 years was rated by two Dunedin Research Unit staff members based on review of birth records and assessment dossiers, including clinical assessments and reports of infections, diseases, injuries, hospitalizations, and other health problems collected during standardized maternal interviews. Ratings used a 5-point scale (inter-rater agreement 0.85). SES (socioeconomic status) was defined as the average highest occupational status level of either parent across study assessments (1=unskilled laborer; 6=professional), from the study member's birth through 15 years, on New Zealand's occupational rating of the 1970s.

Table 3. Physical Health Measures at Age 38.

Measure	Description of Measure	Continuous Outcome: Mean and Standard Deviation	Dichotomous Outcome: Clinical Cutoffs and Prevalence for Females, Males
Periodontal Health	Examinations were conducted in all 4 quadrants using calibrated dental examiners; 3 sites (mesiobuccal, buccal, and distolingual) per tooth were examined, and gingival recession (the distance in millimeters from the cemento-enamel junction to the gingival margin) and probing depth (the distance from the gingival margin to the base of the pocket) were recorded using a PCP-2 probe. The attachment loss for each site was computed by summing gingival recession and probing depth (third molars were not included).	Mean attachment loss across all sites (combined attachment loss in millimeters): M=1.61, SD=0.74	Periodontal Disease: 1+ site(s) with 5 or more mm of attachment loss;[12] 18%, 28%
Lung Function	Spirometry was performed before and after 200 mcg salbutamol inhaled via large-volume spacer. The best FEV_1 (forced expiratory volume) and FVC (forced vital capacity) values from three acceptable and reproducible maneuvers were used.[35]	Post-bronchodilator FEV_1/FVC ratio after 200 mg salbutamol: M=79.95, SD=6.46	Chronic obstructive pulmonary disease (airflow obstruction): FEV_1/FVC ratio < 0.70;[36] 5%, 9%
Systemic Inflammation	Elevation in inflammation was assessed by assaying high-sensitivity C-reactive protein (mg/L). C-reactive protein level is thought to be one of the most reliable measured indicators of vascular inflammation and has been recently endorsed as an adjunct to traditional risk factor screening for cardiovascular risk. High-sensitivity C-reactive protein was measured on a Modular P analyzer (Roche Diagnostics, GmbH, D-68298, Mannheim, Germany) using a particle-enhanced immunoturbidimetric assay.	C-Reactive Protein Level (mg/L): M=2.43, SD=3.82	High C-reactive Protein: > 3 mg/L;[37] 26%, 15%

Table 3 Continued.

Measure	Description of Measure	Continuous Outcome: Mean and Standard Deviation	Dichotomous Outcome: Clinical Cutoffs and Prevalence for Females, Males
Metabolic Syndrome	Metabolic syndrome was assessed with five risk factor biomarkers: (i) high waist circumference, (ii) low high density lipoprotein cholesterol, (iii) high triglycerides, (iv) high blood pressure, and (v) high glycated hemoglobin. Study members with 3+ risk factors were defined as having the metabolic syndrome, per ATPIII guidelines (http://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf).[39] Dichotomous clinical cutoffs for the five biomarkers for metabolic syndrome are provided below.	-	Metabolic Syndrome: 3+ risks; 11%, 21%
Waist Circumference	Waist circumference (in centimeters).	Waist circumference in centimeters: M=86.41, SD=12.65	High Waist Circumference (Biomarker for Metabolic Syndrome): >88 cm for women or > 102 cm for men; 25%, 16%[a]
High Density Lipoprotein (HDL)	Measured via blood in units of mmol/L using colorimetric assay on a Modular P analyzer.	HDL level (mmol/L): M=1.44, SD=0.42	Low HDL (Biomarker for Metabolic Syndrome): <1.3 mmol/L (50 mg/dL) for women or < 1.04 mmol/L (40 mg/dL) for men; 25%, 26%[a,b]

Table 3 Continued.

Measure	Description of Measure	Continuous Outcome: Mean and Standard Deviation	Dichotomous Outcome: Clinical Cutoffs and Prevalence for Females, Males
Triglyceride	Measured via blood in units of mmol/L using colorimetric assay on a Modular P analyzer.	Triglyceride level (mmol/L): M=2.06, SD=1.45	High Triglycerides (Biomarker for Metabolic Syndrome): ≥2.26 mmol/L (200 mg/dL); 14%, 50%[a,b]
Blood Pressure	Assessed according to standard protocols with a Hawksley random-zero sphygmomanometer with a constant deflation valve.[38]	Systolic: M=120.26, SD=12.14; Diastolic: M=78.16, SD=9.93	High Blood Pressure (Biomarker for Metabolic Syndrome): ≥ 130 mm Hg for systolic or ≥ 85 mm Hg for diastolic; 16%, 38%[a]
Glycated Hemoglobin Concentration (HbA1c)	Glycated hemoglobin concentrations (expressed as a percentage of total hemoglobin) were measured by ion exchange high-performance liquid chromatography (Variant II; Bio-Rad, Hercules, CA) (coefficient of variation, 2.4%), a method certified by the U.S. National Glycohemoglobin Standardization Program (NGSP; http://www.ngsp.org/).	HbA1c (% of total hemoglobin): M=5.41, SD=0.54	High Glycated Hemoglobin (Biomarker for Metabolic Syndrome): Scores ≥ 5.7%; 14%, 23%[c]
Body Mass Index (BMI)	Height was measured to the nearest millimeter using a portable Harpenden Stadiometer (Holtain, Crymych, United Kingdom). Weight was recorded to the nearest 0.1 kg using calibrated scales. Body mass index was measured as weight in kilograms divided by height in meters squared.	BMI: M=27.19, SD=5.31	Obese: BMI ≥ 30; 25%, 23%

Table 3 Continued.

Measure	Description of Measure	Continuous Outcome: Mean and Standard Deviation	Dichotomous Outcome: Clinical Cutoffs and Prevalence for Females, Males
Self-Reported Health	Study members were asked: "In general, would you say your health is excellent, very good, good, fair, or poor?" Responses range from 5=excellent, to 1=poor.	Self-Reported Health Mean Rating: M=3.82, SD=0.85	Bad Health: Self ratings of fair or poor health; 5%, 8%

Note. [a]On the basis of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). See http://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf [b]We controlled the diets of all study members and obtained non-fasting lipids. Recent research suggests that fasting is unnecessary for lipids tests.[40-44] We used the American Heart Association's recommended cutoff of 200 mg/dL for non-fasting triglycerides. [c]On the basis of the NGSP clinical advisory committee 2010 recommendation. See http://www.ngsp.org/cac2010.asp

Table 4. Associations of tobacco and cannabis use from age 18 to 38 with age 38 physical health measures.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c]					
							Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
A. Periodontal Health												
Categorical: % with 1+ Sites of >5mm Attachment Loss	Pack-years	12.26	16.00	20.74	36.29	52.89	**1.63**	**1.51, 1.77**	**<.001**	**1.53**	**1.38, 1.70**	**<.001**
	Joint-Years	13.53	21.21	51.45	51.23	55.61	**1.36**	**1.27, 1.46**	**<.001**	**1.11**	**1.02, 1.22**	**.020**
	Cannabis Dependence	13.53	21.30	32.62	47.89	59.72	**1.44**	**1.32, 1.57**	**<.001**	**1.13**	**1.02, 1.26**	**.024**
Continuous: Mean Attachment Loss Across Sites (mm)	Pack-years	1.37	1.44	1.63	1.79	2.32	**0.50**	**0.45, 0.56**	**<.001**	**0.45**	**0.38, 0.51**	**<.001**
	Joint-Years	1.41	1.57	2.08	2.21	2.51	**0.33**	**0.26, 0.39**	**<.001**	**0.12**	**0.05, 0.18**	**<.001**
	Cannabis Dependence	1.41	1.57	1.75	2.06	2.58	**0.33**	**0.27, 0.39**	**<.001**	**0.09**	**0.02, 0.16**	**.011**

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c]					
							Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
B. Lung Function												
Categorical: % with COPD ($FEV_1/FVC < 70$)	Pack-years	5.06	7.93	6.54	7.80	10.55	**1.30**	**1.06, 1.59**	**.010**	**1.26**	**1.01, 1.56**	**.038**
	Joint-Years	5.26	6.81	11.33	10.81	9.75	1.18	0.98, 1.42	.075	1.06	0.87, 1.29	.58
	Cannabis Dependence	5.24	6.68	9.05	9.01	12.73	1.23	1.00, 1.52	.053	1.09	0.85, 1.40	.48
Continuous: $FEV_1/FVC^{\pm}$	Pack-years	80.98	79.74	79.78	79.67	77.58	**-0.19**	**-0.26, -0.13**	**<.001**	**-0.15**	**-0.22, -0.08**	**<.001**
	Joint-Years	80.72	80.15	77.95	78.09	76.43	**-0.17**	**-0.23, -0.11**	**<.001**	**-0.10**	**-0.17, -0.02**	**.010**
	Cannabis Dependence	80.72	80.17	78.93	78.47	76.47	**-0.15**	**-0.22, -0.08**	**<.001**	-0.06	-0.14, 0.01	.106

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c] Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
C. Systemic Inflammation												
Categorical: % with High C-Reactive Protein (>3 mg/L)	Pack-years	18.41	13.94	33.36	17.66	27.93	**1.17**	**1.04, 1.31**	**.007**	**1.16**	**1.02, 1.32**	**.023**
	Joint-Years	20.26	19.66	24.95	30.90	22.02	1.09	0.97, 1.23	.145	1.01	0.88, 1.16	.88
	Cannabis Dependence	20.26	19.60	22.66	29.53	22.96	1.08	0.95, 1.23	.26	0.98	0.85, 1.13	.79
Continuous: C-Reactive Protein Level (mg/L)	Pack-years	2.32	1.70	3.20	2.05	3.17	**0.12**	**0.05, 0.18**	**<.001**	**0.12**	**0.04, 0.19**	**.002**
	Joint-Years	2.48	2.33	2.09	4.01	2.28	0.06	-0.01, 0.13	.073	0.00	-0.07, 0.08	.95
	Cannabis Dependence	2.48	2.36	2.24	3.24	2.64	0.04	-0.02, 0.11	.21	-0.03	-0.11, 0.05	.46

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c] Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
D. Metabolic Health												
Categorical: % with Metabolic Syndrome	Pack-years	14.32	13.12	15.86	15.16	23.16	**1.18**	**1.04, 1.35**	**.012**	**1.24**	**1.06, 1.45**	**.006**
	Joint-Years	18.91	14.23	15.38	21.79	13.53	1.01	0.88, 1.16	.94	0.90	0.76, 1.07	.23
	Cannabis Dependence	18.88	13.27	19.49	26.54	10.99	0.99	0.85, 1.15	.88	0.86	0.73, 1.02	.092
Continuous: Waist (cm)	Pack-years	86.70	85.47	87.84	86.69	85.64	-0.02	-0.08,0.04	.55	0.02	-0.05, 0.09	.56
	Joint-Years	88.15	86.00	84.57	84.97	82.93	**-0.07**	**-0.13, -0.01**	**.029**	**-0.08**	**-0.15, -0.01**	**.026**
	Cannabis Dependence	88.12	85.53	87.56	85.81	83.77	**-0.07**	**-0.13, -0.01**	**.038**	**-0.08**	**-0.15, -0.01**	**.033**
Continuous: High Density Lipoprotein (HDL) Level±	Pack-years	1.46	1.48	1.43	1.45	1.38	**-0.06**	**-0.13, -0.01**	**.036**	**-0.10**	**-0.17, -0.03**	**.004**
	Joint-Years	1.40	1.45	1.58	1.56	1.35	0.03	-0.03, 0.09	.39	**0.08**	**0.01, 0.15**	**.029**
	Cannabis	1.40	1.47	1.43	1.39	1.48	0.03	-0.03, 0.09	.36	**0.09**	**0.01, 0.16**	**.019**

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c] Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
Continuous: Triglyceride Level (mmol/L)	Pack-years	1.99	1.99	2.08	2.27	2.22	**0.07**	**0.01, 0.13**	**.021**	**0.11**	**0.04, 0.17**	**.002**
	Joint-Years	2.12	2.07	1.88	1.98	1.84	-0.03	-0.09, 0.03	.38	**-0.08**	**-0.15, -0.01**	**.019**
	Cannabis Dependence	2.12	2.02	2.02	2.56	1.77	-0.02	-0.08, 0.04	.51	**-0.08**	**-0.15, -0.01**	**.027**
Continuous: Systolic Blood Pressure (mm Hg)	Pack-years	120.92	119.26	118.04	122.01	119.51	-0.02	-0.09, 0.04	.44	-0.01	-0.08, 0.06	.71
	Joint-Years	121.33	119.68	120.69	121.93	117.20	-0.02	-0.08, 0.04	.53	-0.01	-0.08, 0.06	.69
	Cannabis Dependence	121.34	119.73	120.54	120.62	117.50	-0.05	-0.12, 0.01	.101	-0.06	-0.13, 0.02	.127
Continuous: Diastolic Blood Pressure (mm Hg)	Pack-years	78.64	77.19	77.27	78.13	78.20	0.00	-0.06, 0.06	.98	0.01	-0.06, 0.08	.68
	Joint-Years	79.42	77.55	77.70	79.13	76.40	-0.01	-0.08, 0.05	.69	-0.02	-0.09, 0.05	.57
	Cannabis Dependence	79.42	77.44	79.37	77.86	75.80	-0.06	-0.13, 0.00	.056	**-0.09**	**-0.16, -0.01**	**.019**

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c] Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
Continuous: HbA1c	Pack-years	5.40	5.33	5.36	5.37	5.53	**0.11**	**0.05, 0.18**	**<.001**	**0.15**	**0.08, 0.23**	**<.001**
	Joint-Years	5.48	5.37	5.39	5.43	5.36	0.00	-0.07, 0.06	.94	**-0.08**	**-0.15, -0.01**	**.037**
	Cannabis Dependence	5.48	5.36	5.40	5.45	5.38	-0.03	-0.10, 0.03	.34	**-0.13**	**-0.20, -0.05**	**.001**
E. Obesity												
Categorical: % with Body Mass Index ≥ 30	Pack-years	24.76	23.49	31.16	21.12	22.38	0.98	0.87, 1.10	.69	1.02	0.89, 1.17	.78
	Joint-Years	31.20	21.98	24.54	22.88	13.70	0.90	0.79, 1.04	.154	0.89	0.76, 1.05	.169
	Cannabis Dependence	31.23	22.19	20.57	25.64	14.43	**0.85**	**0.74, 0.97**	**.021**	**0.82**	**0.70, 0.95**	**.010**
Continuous: Body Mass Index (BMI)	Pack-Years	27.50	26.80	27.89	27.30	26.32	-0.06	-0.12, 0.00	.066	-0.02	-0.10, 0.05	.51
	Joint-Years	28.22	26.92	26.26	26.38	25.59	**-0.09**	**-0.15, -0.02**	**.011**	-0.07	-0.15, 0.00	.050
	Cannabis Dependence	28.21	26.82	27.10	26.59	25.75	**-0.11**	**-0.17, -0.04**	**.002**	**-0.10**	**-0.18, -0.03**	**.009**

Table 4 Continued.

		% or Mean As a Function of Use, Adjusted for Sex[b]					Statistical Tests[c] Model 1[d]: Bivariate			Model 2[d]: + Control for Pack-Years (or Joint-Years)		
Age 38 Health[a]	Predictor	Never Used	<5 y/ No Dx	5 to <10 y/ 1 Dx	10 to <15 y/ 2 Dx	15+y/ 3+ Dx	(RR or β)	95% CI	p	(RR or β)	95% CI	p
F. Self-Reported Health												
Categorical: % with Bad Health (rating of fair or poor)	Pack-years	4.72	3.97	9.88	7.61	12.55	**1.51**	**1.26, 1.82**	**<.001**	**1.48**	**1.17, 1.87**	**.001**
	Joint-Years	6.34	5.79	11.35	13.04	12.77	**1.26**	**1.06, 1.49**	**.010**	1.04	0.83, 1.30	.75
	Cannabis Dependence	6.32	5.19	11.31	13.60	13.16	**1.28**	**1.03, 1.58**	**.023**	1.01	0.78, 1.32	.92
Continuous: Mean Health Rating±	Pack-years	3.97	3.96	3.72	3.70	3.43	**-0.27**	**-0.33, -0.21**	**<.001**	**-0.26**	**-0.32, -0.19**	**<.001**
	Joint-Years	3.86	3.88	3.53	3.46	3.47	**-0.15**	**-0.22, -0.09**	**<.001**	-0.03	-0.10, 0.04	.42
	Cannabis Dependence	3.86	3.91	3.55	3.55	3.27	**-0.16**	**-0.23, -0.10**	**<.001**	-0.03	-0.11, 0.04	.40

Note: COPD=chronic obstructive pulmonary disease. a. Results are presented for categorically-scored (for clinical relevance) and continuously scored (for greater sensitivity to variation) versions of the health measures. b. For presentation of percentages and means, participants were grouped according to pack-years and joint-years between ages 18-38 as follows: never used, used <5 years, used from 5 to <10 years, used from 10 to <15 years, and used for 15+ years. Participants were grouped according to persistence of cannabis dependence as follows: never used=never used cannabis, no dx=used cannabis at least once between ages 18-38 but never diagnosed, 1 dx= diagnosed once between ages 18-38, 2 dx=diagnosed twice, 3+ dx=diagnosed 3+ times. c. Statistical analyses tested associations of cumulative pack-years (a continuous variable), cumulative joint-years (a continuous variable), and cannabis dependence (a 5-level ordinal variable) with dichotomous and continuous outcomes.

Relative risks are reported for dichotomous outcomes. Beta coefficients are reported for continuous outcomes. Continuous variables were standardized for statistical tests. Therefore, relative risks and beta coefficients can be interpreted as the increase in risk of the outcome, given a 1 SD increase pack-years or joint-years. Relative risks greater than 1 and betas with a positive sign indicate poorer health except where noted. ±Betas with a negative sign indicate poorer health. Statistically significant associations are shown in bold. d. Model 1 controls for sex. Model 2 adds controls for joint-years in analyses of pack-years, and adds controls for pack-years in analyses of joint-years and cannabis dependence. Analyses of lung function additionally control for height. For analyses of tobacco pack-years, Ns range from 892-945 for Model 1 and 886-938 for Model 2. For analyses of cannabis joint-years and cannabis dependence, Ns range from 888-940 for Model 1 and 886-938 for Model 2. The reasons for different Ns across analyses is that there was some variation in missingness for specific health measurements. Among the 947 study members included in this report, n=47 refused the dental exam, n=28 did not complete the lung function assessment, n=35 refused phlebotomy, 9 were pregnant, 6 HbA1c samples were lost in the laboratory due to the 2011 Christchurch earthquake, and there were a handful of miscellaneous assay failures.

Table 5. Within-individual change in health from age 26 to 38: associations between tobacco and cannabis use from ages 26-38 and age 38 health, controlling for age 26 baseline health.

		Model 1: Bivariate			Model 2: + Control for Baseline at Age 26			Model 3[b]: + Control for Joint-Years (or Pack-Years)		
Age 38 Health[a]	Exposure	(RR or β)	95% CI	p	(RR or β)	95% CI	p	(RR or β)	95% CI	p
A. Periodontal Health										
Categorical: % with 1+ Sites of >5mm Attachment Loss	Pack-years	**1.62**	**1.49, 1.75**	**<.001**	**1.59**	**1.47, 1.72**	**<.001**	**1.53**	**1.39, 1.69**	**<.001**
	Joint-Years	**1.32**	**1.23, 1.42**	**<.001**	**1.30**	**1.20, 1.40**	**<.001**	1.08	0.98, 1.18	.110
	Cannabis Dependence	**1.57**	**1.39, 1.77**	**<.001**	**1.54**	**1.37, 1.74**	**<.001**	**1.18**	**1.03, 1.36**	**.015**
Continuous: Mean Attachment Loss Across Sites (mm)	Pack-years	**0.50**	**0.44, 0.56**	**<.001**	**0.42**	**0.36, 0.47**	**<.001**	**0.37**	**0.31, 0.43**	**<.001**
	Joint-Years	**0.32**	**0.25, 0.38**	**<.001**	**0.25**	**0.19, 0.31**	**<.001**	**0.10**	**0.05, 0.16**	**<.001**
	Cannabis Dependence	**0.37**	**0.29, 0.45**	**<.001**	**0.30**	**0.23, 0.38**	**<.001**	**0.11**	**0.04, 0.19**	**.002**

Table 5 Continued.

Age 38 Health[a]	Exposure	Model 1: Bivariate (RR or β)	95% CI	p	Model 2: + Control for Baseline at Age 26 (RR or β)	95% CI	p	Model 3[b]: + Control for Joint-Years (or Pack-Years) (RR or β)	95% CI	p
B. Lung Function										
Categorical: % with COPD ($FEV_1/FVC < 70$)	Pack-years	**1.27**	**1.02, 1.57**	**.030**	**1.27**	**1.05, 1.55**	**.015**	**1.33**	**1.10, 1.62**	**.004**
	Joint-Years	1.13	0.92, 1.39	.24	1.01	0.84, 1.20	.93	0.91	0.78, 1.06	.22
	Cannabis Dependence	1.20	0.92, 1.56	.178	1.18	0.92, 1.53	.199	1.03	0.80, 1.33	.81
Continuous: $FEV_1/FVC^{\pm}$	Pack-years	**-0.19**	**-0.26, -0.12**	**<.001**	**-0.14**	**-0.19, -0.10**	**<.001**	**-0.11**	**-0.16, -0.06**	**<.001**
	Joint-Years	**-0.15**	**-0.21, -0.08**	**<.001**	**-0.11**	**-0.16, -0.07**	**<.001**	**-0.07**	**-0.12, -0.02**	**.008**
	Cannabis Dependence	**-0.17**	**-0.26, -0.09**	**<.001**	**-0.14**	**-0.20, -0.09**	**<.001**	**-0.08**	**-0.15, -0.02**	**.011**

Table 5 Continued.

Age 38 Health[a]	Exposure	Model 1: Bivariate (RR or β)	95% CI	p	Model 2: + Control for Baseline at Age 26 (RR or β)	95% CI	p	Model 3[b]: + Control for Joint-Years (or Pack-Years) (RR or β)	95% CI	p
C. Systemic Inflammation										
Categorical: % with High C-Reactive Protein (>3 mg/L)	Pack-years	**1.16**	**1.02, 1.31**	**.026**	**1.16**	**1.03, 1.32**	**.019**	1.11	0.97, 1.28	.135
	Joint-Years	**1.14**	**1.01, 1.29**	**.038**	**1.16**	**1.03, 1.32**	**.017**	1.11	0.97, 1.28	.145
	Cannabis Dependence	1.17	0.97, 1.40	.093	1.21	1.00, 1.46	.050	1.13	0.92, 1.38	.25
Continuous: C-Reactive Protein Level (mg/L)	Pack-years	**0.11**	**0.04, 0.18**	**.003**	**0.11**	**0.04, 0.17**	**.002**	**0.09**	**0.01, 0.16**	**.021**
	Joint-Years	**0.08**	**0.01, 0.16**	**.026**	**0.09**	**0.02, 0.16**	**.013**	0.05	-0.03, 0.13	.199
	Cannabis Dependence	0.02	-0.07, 0.12	.61	0.04	-0.05, 0.13	.38	-0.02	-0.12, 0.07	.62

Table 5 Continued.

Age 38 Health[a]	Exposure	Model 1: Bivariate (RR or β)	95% CI	p	Model 2: + Control for Baseline at Age 26 (RR or β)	95% CI	p	Model 3[b]: + Control for Joint-Years (or Pack-Years) (RR or β)	95% CI	p
D. Metabolic Health										
Categorical: % with Metabolic Syndrome	Pack-years	**1.18**	**1.03, 1.36**	**.020**	**1.18**	**1.02, 1.35**	**.021**	**1.21**	**1.04, 1.41**	**.014**
	Joint-Years	1.00	0.86, 1.16	.99	1.01	0.88, 1.17	.88	0.93	0.79, 1.10	.41
	Cannabis Dependence	1.02	0.84, 1.26	.80	1.07	0.88, 1.31	.50	0.98	0.79, 1.21	.84
E. Obesity										
Categorical: % with Body Mass Index ≥ 30	Pack-years	0.96	0.84, 1.09	.49	0.96	0.86, 1.08	.49	1.00	0.89, 1.12	.99
	Joint-Years	0.88	0.76, 1.01	.073	0.91	0.80, 1.05	.21	0.91	0.79, 1.06	.24
	Cannabis Dependence	**0.84**	**0.71, 0.99**	**.047**	0.92	0.79, 1.07	.27	0.93	0.80, 1.09	.37
Continuous: Body Mass Index (BMI)	Pack-Years	**-0.07**	**-0.14, -0.01**	**.027**	0.00	-0.04, 0.04	.91	0.02	-0.03, 0.06	.51
	Joint-Years	**-0.09**	**-0.16, -0.03**	**.006**	-0.02	-0.06, 0.02	.35	-0.03	-0.07, 0.02	.25
	Cannabis Dependence	**-0.13**	**-0.21, -0.04**	**.004**	-0.01	-0.07, 0.04	.60	-0.01	-0.07, 0.04	.59

Table 5 Continued.

Age 38 Health[a]	Exposure	Model 1: Bivariate (RR or β)	95% CI	p	Model 2: + Control for Baseline at Age 26 (RR or β)	95% CI	p	Model 3[b]: + Control for Joint-Years (or Pack-Years) (RR or β)	95% CI	p
F. Self-Reported Health										
Categorical: % with Bad Health (rating of fair or poor)	Pack-years	**1.54**	**1.29, 1.84**	**<.001**	**1.37**	**1.11, 1.70**	**.004**	**1.37**	**1.08, 1.73**	**.010**
	Joint-Years	1.14	0.94, 1.40	.192	1.08	0.87, 1.33	.49	0.96	0.78, 1.19	.72
	Cannabis Dependence	1.26	0.94, 1.69	.118	1.17	0.88, 1.55	.29	1.00	0.73, 1.37	.99
Continuous: Mean Health Rating[±]	Pack-years	**-0.27**	**-0.33, -0.21**	**<.001**	**-0.16**	**-0.22, -0.10**	**<.001**	**-0.16**	**-0.22, -0.10**	**<.001**
	Joint-Years	**-0.11**	**-0.18, -0.05**	**<.001**	-0.06	-0.11, 0.00	.064	0.01	-0.05, 0.07	.77
	Cannabis Dependence	**-0.17**	**-0.26, -0.09**	**<.001**	**-0.12**	**-0.19, -0.04**	**.002**	-0.04	-0.12, 0.04	.34

Note. COPD=chronic obstructive pulmonary disease. a. Results are presented for categorically-scored (for clinical relevance) and continuously scored (for greater sensitivity to variation) versions of the health measures. b. Model 3 adds controls for joint-years in analyses of pack-years, and adds controls for pack-years in analyses of joint-years and cannabis dependence. Statistical analyses tested associations of cumulative pack-years (a continuous variable), cumulative joint-years (a continuous variable), and cannabis dependence (a 5-level ordinal variable) with dichotomous and continuous outcomes. Relative risks are reported for dichotomous outcomes. Beta coefficients are reported for continuous outcomes. Continuous variables were standardized for statistical tests. Therefore, relative risks and beta coefficients can be interpreted as the increase in risk of the outcome, given a 1 SD increase in pack-years or joint-years. Relative risks greater than 1 and betas with a positive sign indicate poorer health except where noted. [±]Betas with a negative sign indicate poorer health. Statistically significant associations are shown in bold. All models control for sex. Analyses of lung function additionally control for height.